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Probiotics for preventing gestational diabetes (Review)

Barrett HL, Dekker Nitert M, Conwell LS, Callaway LK

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[Intervention Review]

Probiotics for preventing gestational diabetes

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ABSTRACT

Background

Gestational diabetes mellitus (GDM) is associated with a range of adverse pregnancy outcomes for mother and infant. The prevention of GDM using lifestyle interventions has proven difficult. The gut microbiome (the composite of bacteria present in the intestines) influences host inflammatory pathways, glucose and lipid metabolism and, in other settings, alteration of the gut microbiome has been shown to impact on these host responses. Probiotics are one way of altering the gut microbiome but little is known about their use in influencing the metabolic environment of pregnancy.

Objectives

To assess the effects of probiotic supplementation when compared with other methods for the prevention of GDM.

Search methods

We searched the Cochrane Pregnancy and childbirth Group's Trials Register (31 August 2013) and reference lists of the articles of retrieved studies.

Selection criteria

Randomised and cluster-randomised trials comparing the use of probiotic supplementation with other methods for the prevention of the development of GDM. Cluster-randomised trials were eligible for inclusion but none were identified. Quasi-randomised and cross-over design studies are not eligible for inclusion in this review. Studies presented only as abstracts with no subsequent full report of study results would also have been excluded.

Data collection and analysis

Two review authors independently assessed study eligibility, extracted data and assessed risk of bias of included study. Data were checked for accuracy.

Main results

Eleven reports (relating to five possible trials) were found. We included one study (six trial reports) involving 256 women. Four other studies are ongoing.

The included trial consisted of three treatment arms: probiotic with dietary intervention, placebo and dietary intervention, and dietary intervention alone; it was at a low risk of bias. The study reported primary outcomes of a reduction in the rate of gestational diabetes

mellitus (risk ratio (RR) 0.38, 95% confidence interval (CI) 0.20 to 0.70), with no statistical difference in the rates of miscarriage/intrauterine fetal death (IUFD)/stillbirth/neonatal death (RR 2.00, 95% CI 0.35 to 11.35). Secondary outcomes reported were a reduction in infant birthweight (mean difference (MD) -127.71 g, 95% CI -251.37 to -4.06) in the probiotic group and no clear evidence of increased risk of preterm delivery (RR 3.27, 95% CI 0.44 to 24.43), or caesarean section rate (RR 1.23, 95% CI 0.65 to 2.32). The primary infant outcomes of rates of macrosomia and large-for-gestational age infants were not reported. The following secondary outcomes were not reported: maternal gestational weight gain, pre-eclampsia, and the long-term diagnosis of diabetes mellitus; infant body composition, shoulder dystocia, admission to neonatal intensive care, jaundice, hypoglycaemia and long-term rates of obesity and diabetes mellitus.

Authors' conclusions

One trial has shown a reduction in the rate of GDM when women are randomised to probiotics early in pregnancy but more uncertain evidence of any effect on miscarriage/IUFD/stillbirth/neonatal death. There are no data on macrosomia. At this time, there are insufficient studies to perform a quantitative meta-analysis. Further results are awaited from four ongoing studies.

PLAIN LANGUAGE SUMMARY

Probiotics to prevent gestational diabetes mellitus

Gestational diabetes mellitus is a condition where the mother has high blood sugar levels during pregnancy. It is associated with a range of adverse pregnancy outcomes for the mother, such as pre-eclampsia (high blood pressure with protein in the urine) and instrumental or operative delivery, as well as for the infants who may be born large-for-gestational age. Current treatment includes diet with or without medication. Prevention of this condition would be preferable to treatment. Preventative diet and lifestyle interventions are time consuming and do not always reduce the number of women getting gestational diabetes. Probiotics - 'good' bacteria that are usually taken in the form of capsules or drinks - supplement the gut bacteria. They have the potential to change a person's metabolism and so prevent gestational diabetes mellitus. This review was designed to look at whether there is evidence to show if this is true or not. At the moment there is only one randomised controlled study, which involved 256 women. This study does show a lower rate of gestational diabetes mellitus in women who took probiotics from early pregnancy, with the rate of diagnosis of gestational diabetes mellitus being reduced by two-thirds and their babies on average weighed 127 g less at birth. This study did not find differences in the rates of miscarriage, intrauterine or neonatal death or stillbirth. There was no clear evidence of a change in the proportion of women delivered by caesarean section or in the risk of preterm delivery. The study did not report on how much weight the mothers gained during pregnancy or how many babies were large-for-gestational age or that weighed more than 4000 g at birth or on the body composition of the babies. One study is not enough to draw any definite conclusions at the moment. There are other studies underway.

BACKGROUND

Description of the condition

Gestational diabetes mellitus (GDM) is currently defined as carbohydrate intolerance first diagnosed during pregnancy (Hadar 2009). There are a number of different diagnostic criteria world wide (Table 1). Rates of GDM are increasing in the obstetric population of both the developed (ACOG Committee 2005; Moore 2010) and developing world (Hossain 2007; Seshiah 2008), driven by increasing rates of overweight and obesity. Applying the new International Association of the Diabetes and Pregnancy Study Groups (IADPSG) diagnostic criteria, 18% of pregnancies in the United States are affected by GDM (HAPO 2008). India and other developing nations are also seeing an increase with rates varying from ~ 18% in urban populations to 10% in rural populations (Seshiah 2008).

GDM is associated with increased rates of maternal and fetal morbidity and mortality, both during the pregnancy and in the longer term (Davey 2005). Maternal pregnancy complications include pre-eclampsia (a syndrome of hypertension and proteinuria) and instrumental or operative delivery. Fetal complications include macrosomia (birthweight greater than 4000 g), polyhydramnios (excessive amniotic fluid), preterm birth, shoulder dystocia (obstruction of vaginal delivery by the infant's shoulder), and neonatal complications of admission to high-level care, respiratory distress, hypoglycaemia (low blood sugar), and jaundice. Both women with GDM and their infants are at increased risk of diabetes mellitus and metabolic dysfunction later in life (Shah 2008; Vohr 2008).

Treatment of GDM improves pregnancy outcomes with significant reductions in the rate of serious perinatal outcomes including macrosomia, shoulder dystocia and caesarean delivery (Crowther 2005; Landon 2009). Current management practices for GDM are expensive but also cost effective for healthcare systems in the short and longer term (Ohno 2011). Primary prevention of GDM rather than treatment would however be ideal in preventing both the economic and health costs associated with GDM.

Efforts to prevent GDM have focused on lifestyle interventions (including diet and exercise) (Chuang 2010). These interventions have proven challenging, both to perform and in the analysis of effect due to heterogeneity, small study size, limited patient adherence to the intervention and methodological issues. Also, it is known that adherence to even simple measures such as folate supplementation is poor (Callaway 2009). Recent systematic reviews have concluded that no firm statement on the utility of nutritional interventions in controlling maternal weight or preventing GDM can be made (Dodd 2010; Streuling 2010). A Cochrane review examining the use of dietary advice in pregnancy for prevention of GDM has found that a low glycaemic diet was beneficial for some outcomes including a reduced rate of large-for-gestational-age infants; the results from the review were inconclusive (Tieu 2008). Another Cochrane review examining the utility of exercise is currently underway (Han 2011). Therefore, even if complex lifestyle intervention strategies were shown to prevent GDM, compliance with these interventions for the general population would be low. If probiotic supplementation were shown to be an effective method of reducing rates of GDM, there would be considerable benefits through improving maternal health and reducing pregnancy complications as well as a potential reduction in health service costs related to the management of GDM.

Description of the intervention

The World Health Organization defines probiotics as "microorganisms ... able to confer defined health benefits on the host" (FAO/WHO 2001). Most probiotic products are either in food items (such as fermented milks or yogurts available in the supermarkets) or supplied as dietary supplements that typically are for sale in health food stores, pharmacies or natural food grocery stores. These products vary considerably in their microbial composition and number (dosage) of viable bacteria. Interventions of oral intake of probiotics in any form during pregnancy will be included for the review.

How the intervention might work

The relationship between diet, host metabolism and gut microbiome (the variety of bacterial strains in the gut) is multidirectional. Diet can influence microbiotal composition and gene expression as well as altering host metabolism directly. Altering the gut microbiome directly can also influence the host, including altering ease of nutrient absorption (Turnbaugh 2006), and influencing host inflammatory pathways, glucose and lipid metabolism (Backhed 2004; Musso 2010). Inflammation has been implicated in preterm labour and probiotics have been used in the prevention of preterm labour with inconclusive results (Othman 2007).

Obesity (Backhed 2009) and type 2 diabetes (Larsen 2010) are associated with divergent changes in the gut microbiome (the composite of bacteria present in the intestines). The gut microbiome in obese rodents and humans shows an overall decrease in microbiotal diversity, with an increase in *Firmicutes* phylum of bacteria, mainly of the *Mollicutes* class and a fall in the species belonging to the *Bacteroidetes* phylum of bacteria (Turnbaugh 2008; Turnbaugh 2009). Patients with type 2 diabetes have significantly reduced numbers of species belonging to the *Firmicutes* phylum. The ratio of *Bacteroidetes*:*Firmicutes* species in type 2 diabetes correlates positively with plasma glucose concentration but not body mass index. *Bacteroidetes* species are Gram negative bacteria, containing lipopolysaccharides in their outer wall, which could contribute to insulin resistance (Larsen 2010). A trial of supplementation of the probiotic strain *Lactobacillus acidophilus* NCFM™ in men with type 2 diabetes showed a preservation of insulin sensitivity but no change in inflammatory markers over a four-week period (Andreasen 2010). Improvements in glycaemia and lipids have been reported in other trials of probiotics in type 2 diabetes (Ejtahed 2012; Moroti 2012). Women with GDM are known to be at high risk of developing type 2 diabetes, and have a similar abnormal insulin resistance and alteration in lipid metabolism (Davey 2005). The gut microbiome has not been explored in GDM.

Why it is important to do this review

A recent study examining probiotics in pregnancy suggested a benefit in reducing the incidence of gestational diabetes (Laitinen 2008). Gestational diabetes is increasingly common and carries significant risks for both maternal and infant health. Other types of interventions, such as diet and exercise have proven difficult to carry out and have mixed results (Dodd 2010; Streuling 2010). Implementation of these interventions on a large scale practical clinical level would prove challenging and expensive. Probiotic supplementation, if beneficial, would be much easier to use in clinical practice. A systematic review of the available literature is required to establish whether there is any evidence to support the use of probiotic supplements during pregnancy for preventing gestational diabetes.

OBJECTIVES

To systematically assess the effects of probiotic supplements used either alone or in combination with pharmacological and non-pharmacological interventions on the incidence of gestational diabetes.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised and cluster-randomised trials. Cluster-randomised trials were eligible for inclusion but none were identified. Quasi-randomised and cross-over design studies are not eligible for inclusion in this review. Studies presented only as abstracts with no subsequent full report of study results would also have been excluded.

Types of participants

Studies that included pregnant women not previously diagnosed with diabetes mellitus. Studies of women with GDM in a previous pregnancy but no evidence of diabetes mellitus or GDM in the current pregnancy before entering the trial were eligible for inclusion.

Types of interventions

Probiotic supplementation for prevention of gestational diabetes, either alone or in combination with pharmacological (e.g. metformin) or non-pharmacological interventions (e.g. diet/lifestyle interventions).

Probiotic supplementation (administered by any method) should have been commenced prior to the diagnosis of gestational diabetes and continued for any duration.

Comparison interventions of any type were eligible, e.g. placebo, diet, exercise, pharmacological therapy (e.g. metformin).

Trials may have used other interventions in a comparison arm or in combination with the probiotic. These other interventions may have included pharmaceutical probiotic supplements as well as food items supplemented with probiotics.

Types of outcome measures

Primary outcomes

Maternal

- Diagnosis of gestational diabetes mellitus, by the local criteria where the study was performed.

Infant

- Macrosomia and large-for-gestational age.
- Death (including intrauterine fetal death (IUFD), stillbirth and neonatal death).

Secondary outcomes

Maternal

- Pre-eclampsia.
- Changes in maternal gestational weight gain.
- Preterm delivery.
- Caesarean section.
- Long-term outcome - diagnosis of diabetes mellitus.

Infant

- Birthweight/birth centile, body composition.
- Shoulder dystocia.
- Admission to neonatal intensive care.
- Jaundice.
- Hypoglycaemia.
- Longitudinal data - rates of obesity, rates of diabetes mellitus, body composition.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (31 August 2013).

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE;
3. weekly searches of Embase;
4. handsearches of 30 journals and the proceedings of major conferences;
5. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL, MEDLINE and Embase, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.

Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

Searching other resources

We searched the reference lists of all retrieved studies.

We did not apply any language restrictions.

Data collection and analysis

Selection of studies

Two review authors (Helen Barrett and Marloes Dekker Nitert) independently assessed for inclusion all the potential studies we identified as a result of the search strategy. We resolved any disagreement through discussion or, if required, we consulted review author Leonie Callaway.

Data extraction and management

We designed a form to extract data. For the one eligible study, two review authors extracted the data using the agreed form. There

were no discrepancies in data extraction on the form. We entered data into Review Manager software (RevMan 2012) and checked it for accuracy.

All information regarding any of the above was clear, and we made no attempt to contact authors of the original report to provide further details.

Assessment of risk of bias in included studies

Two review authors (HLB, MDN) independently assessed risk of bias for the one included study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (*Handbook*) (Higgins 2011). We resolved any disagreement by discussion or by involving a third assessor.

(1) Random sequence generation (checking for possible selection bias)

We described the method used to generate the allocation sequence in sufficient detail to assess whether it produced comparable groups.

We assessed the method as:

- low risk of bias (any truly random process, e.g. random number table; computer random number generator);
- high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
- unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)

We described the methods used to conceal allocation to interventions prior to assignment and assessed whether the intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We assessed the methods as:

- low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk of bias.

(3.1) Blinding of participants and personnel (checking for possible performance bias)

We described the methods used to conceal the allocation sequence and determine whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.
We assessed the methods as:

- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel.

(3.2) Blinding of outcome assessment (checking for possible detection bias)

We described the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We considered that studies would be at low risk of bias if they were blinded, or if we judged that the lack of blinding would be unlikely to affect results. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed the methods as:

- low, high or unclear risk of bias.

(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

For the included study, we described, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We stated whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported, or could be supplied by the trial authors, we re-included missing data in the analyses which we undertook.

We assessed methods as:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation);
- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

We described how we investigated the possibility of selective outcome reporting bias and what we found.
We assessed the methods as:

- low risk of bias (where it is clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias.

(6) Other bias (checking for bias due to problems not covered by (1) to (5) above)

We described any important concerns we had about other possible sources of bias.
We assessed whether the included study was free of other problems that could put it at risk of bias:

- low risk of other bias;
- high risk of other bias;
- unclear whether there is risk of other bias.

(7) Overall risk of bias

We made explicit judgements about whether the included study was at high risk of bias, according to the criteria given in the *Hand-*

book (Higgins 2011). With reference to (1) to (6) above, we assessed the likely magnitude and direction of the bias and whether we considered it was likely to impact on the findings. We planned to explore the impact of the level of bias through undertaking sensitivity analyses - see Sensitivity analysis.

Measures of treatment effect

Dichotomous data

For dichotomous data, we present results as summary risk ratio with 95% confidence intervals.

Continuous data

For continuous data, we used the mean difference if outcomes were measured in the same way between trials. We planned to use the standardised mean difference to combine trials that measure the same outcome, but used different scales.

Unit of analysis issues

Cluster-randomised trials

We did not identify any cluster-randomised trials for inclusion. However, if we identify cluster-randomised trials in future updates of this review, we will include cluster-randomised trials in the analyses along with individually-randomised trials. We will adjust their effect measure using the methods described in the *Handbook* using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population. Where the cluster-randomised trial properly accounts for the cluster design, we will extract an estimate of the effect measure directly. Where the cluster-randomised trial does not properly account for the clustering, we will calculate the effective sample size of the intervention and placebo groups by dividing the sample size by the design effect. The design effect is 1+ (m-1)*ICC where the ICC is the intracluster correlation co-efficient and m the average cluster size. The assessment of cluster-randomised trials and the calculation of the effective sample size will be performed with the assistance of a statistician. If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomised trials and individually-randomised trials, we plan to synthesise the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely.

We will also acknowledge heterogeneity in the randomisation unit and perform a subgroup analysis to investigate the effects of the randomisation unit.

Dealing with missing data

The one included study had a low level of attrition over the follow-up period of 12 months postpartum of 18.75%. In future updates, we will explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis.

For all outcomes, we carried out analyses, as far as possible, on an intention-to-treat basis, i.e. we attempted to include all participants randomised to each group in the analyses, and all participants were analysed in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial was the number randomised minus any participants whose outcomes are known to be missing.

Assessment of heterogeneity

We planned to assess statistical heterogeneity in each meta-analysis using the T^2, I^2 and Chi^2 statistics. We would have regarded heterogeneity as substantial if the I^2 was greater than 30% and either the T^2 was greater than zero, or there was a low P value (less than 0.10) in the Chi^2 test for heterogeneity.

Assessment of reporting biases

Given only one study has reported results, reporting biases analysis has not yet been undertaken. In future updates of this review, if there are 10 or more studies in the meta-analysis we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually. If asymmetry is suggested by a visual assessment, we will perform exploratory analyses to investigate it.

Data synthesis

We carried out statistical analysis using the Review Manager software (RevMan 2012). We planned to use fixed-effect meta-analysis for combining data where it was reasonable to assume that studies were estimating the same underlying treatment effect: i.e. where trials examined the same intervention, and the trials' populations and methods were judged sufficiently similar. As only one study has reported results, heterogeneity analysis has not yet been undertaken. If more studies are included in future updates of this review, and there is clinical heterogeneity sufficient to expect that the underlying treatment effects differ between trials, or if substantial statistical heterogeneity is detected, we will use random-effects meta-analysis to produce an overall summary, if an average treatment effect across trials is considered clinically meaningful. The random-effects summary will be treated as the average range of possible treatment effects and we will discuss the clinical implications of treatment effects differing between trials. If the average treatment effect is not clinically meaningful, we will not combine trials.

If we use random-effects analyses, the results will be presented as the average treatment effect with 95% confidence intervals, and the estimates of T^2 and I^2.

For multi-arm trials, where there is a blinded placebo and unblinded control as well as treatment arm(s), the arms will be compared separately without double counting of participants. Where there is more than one treatment arm, each arm will be compared separately to each of the other arms, without double counting of participants.

Subgroup analysis and investigation of heterogeneity

Given only one study has reported results, subgroup analysis has not yet been undertaken. If we identify substantial heterogeneity in future updates as more trials are included, we will investigate it using subgroup analyses and sensitivity analyses. We will consider whether an overall summary is meaningful, and if it is, use random-effects analysis to produce it.

We plan to carry out the following subgroup analyses.

1. Maternal body mass index (BMI): normal/overweight/obese. Subgroups defined by BMI. BMI will be categorised as underweight (BMI less than 18.49), normal weight (18.5 to 24.99), overweight (25.00 to 29.99), obesity class I (30.00 to 34.99), class II (35.00 to 39.99), class III (greater than 40.00) (WHO 2000; WHO Expert Consultation 2004). (underweight versus normal versus overweight versus obese).
2. Past history of GDM (yes versus no).
3. Family history of type 2 diabetes (yes versus no).
4. Probiotic dose (more than 5 billion colony-forming units (CFU) versus less than 5 billion CFU).
5. Probiotic bacterial species (each species versus others).
6. Probiotic duration of treatment (early pregnancy versus more than 20 weeks).
7. Probiotic mode of delivery (capsule versus other).
8. Probiotic frequency of administration (daily versus other).

Subgroup analysis will be restricted to the review's primary outcomes.

We will assess subgroup differences by interaction tests available within RevMan (RevMan 2012). We will report the results of subgroup analyses quoting the χ^2 statistic and p-value, and the interaction test I^2 value.

Sensitivity analysis

As only one study has reported results, sensitivity analysis has not yet been undertaken. Sensitivity analysis will be carried out, where necessary, to explore the influence of diagnostic criteria for GDM, and high drop-out rates (more than 20%).

RESULTS

Description of studies

Results of the search

The search of the Cochrane Pregnancy and Childbirth Group's Trials Register retrieved eight citations. Review of the reference lists of these studies, and the reference lists of citations found in these studies yielded three further citations. The 11 citations related to five independent randomised controlled trials. Only one of these trials has reported results and has been included (Laitinen 2008). The other four studies are (Ahmed 2012; Callaway 2012; McAuliffe 2012; Wickens 2012) are ongoing (see Characteristics of ongoing studies) (see: Figure 1).

Figure 1. Study flow diagram.

Included studies

Laitinen 2008 is the only study that has reported results and hence is the only included study at this point. The study was a double blind (for probiotics) randomised controlled trial carried out in Finland, with three treatment arms: placebo/diet and placebo/probiotic and diet. It included 256 women, of whom 7% were obese and 21% overweight, without any metabolic or chronic disease. The study duration for the woman was from early pregnancy until the end of exclusive breastfeeding, with follow-up until 24 months postpartum. The probiotic strains used were: *Lactobacillus rhamnosus* GG, ATCC 53 103, Valio Ltd, Helsinki, Finland and *Bifidobacterium lactis* Bb12, Chr. Hansen, Hoersholm, Denmark, 10^{10} colony-forming units/day each). Placebo was microcrystalline cellulose and dextrose anhydrate. The intensive dietary counselling was to conform to the currently recommended pregnancy diet.

Excluded studies

There are no excluded studies.

Risk of bias in included studies

See Characteristics of included studies. The included study was assessed to be at low risk of bias across all risk of bias domains. In the future, when the results of the study that three of the authors of this review are involved in (Helen Barrett, Marloes Dekker Nitert and Leonie Callaway) (Callaway 2012), the fourth author (Louise Conwell) will assess risk of bias with the assistance from the Cochrane Pregnancy and Childbirth Group in order to minimise the effects of conflict of interest.

Allocation

Laitinen 2008 used computer-generated block randomisation of six women in each block. The randomisation list was generated by a non-investigator statistician, and placed in sealed envelopes (Laitinen 2008).

Blinding

Placebo/probiotic allocation was blind to both participants and personnel, however, dietary therapy was not blinded to study staff (Laitinen 2008).

Incomplete outcome data

There was minimal loss to follow-up at the time of testing for gestational diabetes mellitus (Laitinen 2008).

Selective reporting

All findings reported (Laitinen 2008).

Other potential sources of bias

None.

Effects of interventions

Laitinen 2008 is the only currently completed study; the results of the study are described below. We used two comparisons from the three treatment arms in the study (probiotics + diet, placebo + diet and diet alone), halving the sample size and any relevant denominators for binary data from probiotic group data.

Probiotics versus control (diet or placebo)

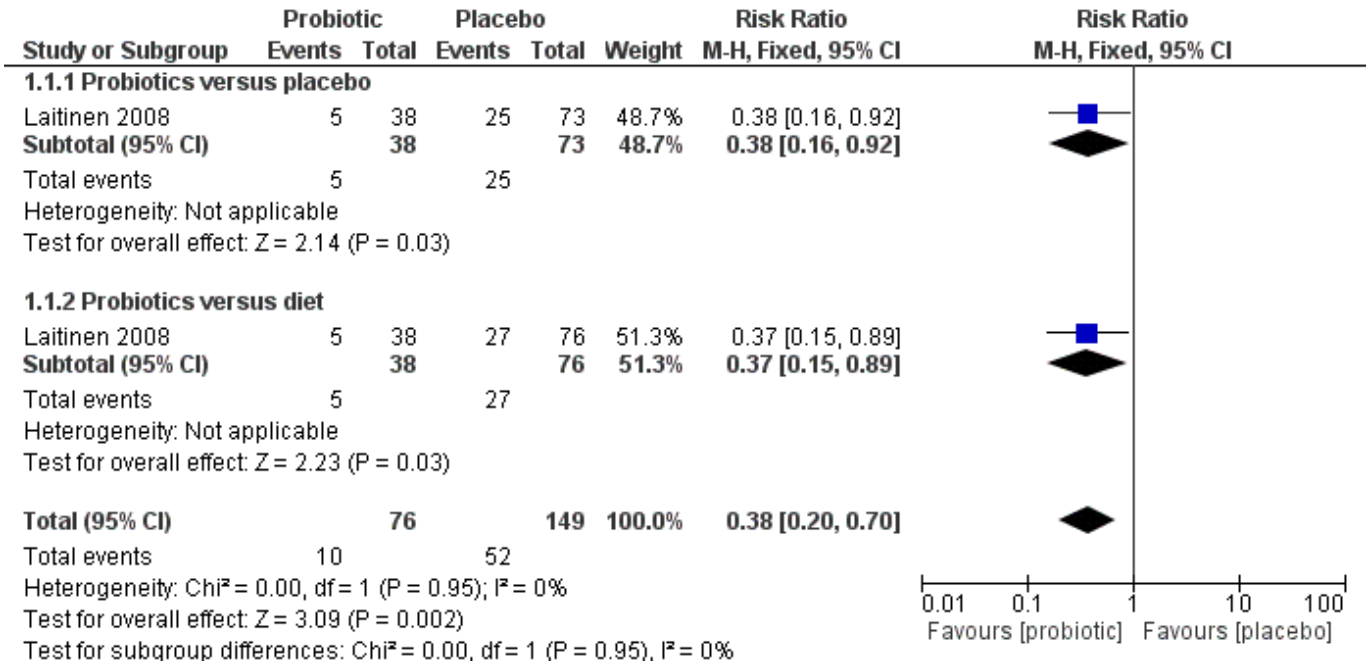
Primary outcomes

Maternal outcome

Diagnosis of gestational diabetes

The use of probiotics was associated with a reduction in the rate of gestational diabetes (risk ratio (RR) 0.38, 95% confidence interval (CI) 0.20 to 0.70) (Analysis 1.1) (Figure 2).

Figure 2. Forest plot of comparison: 1 Primary maternal and infant outcomes: Probiotics vs placebo or diet, outcome: 1.1 Diagnosis of gestational diabetes.

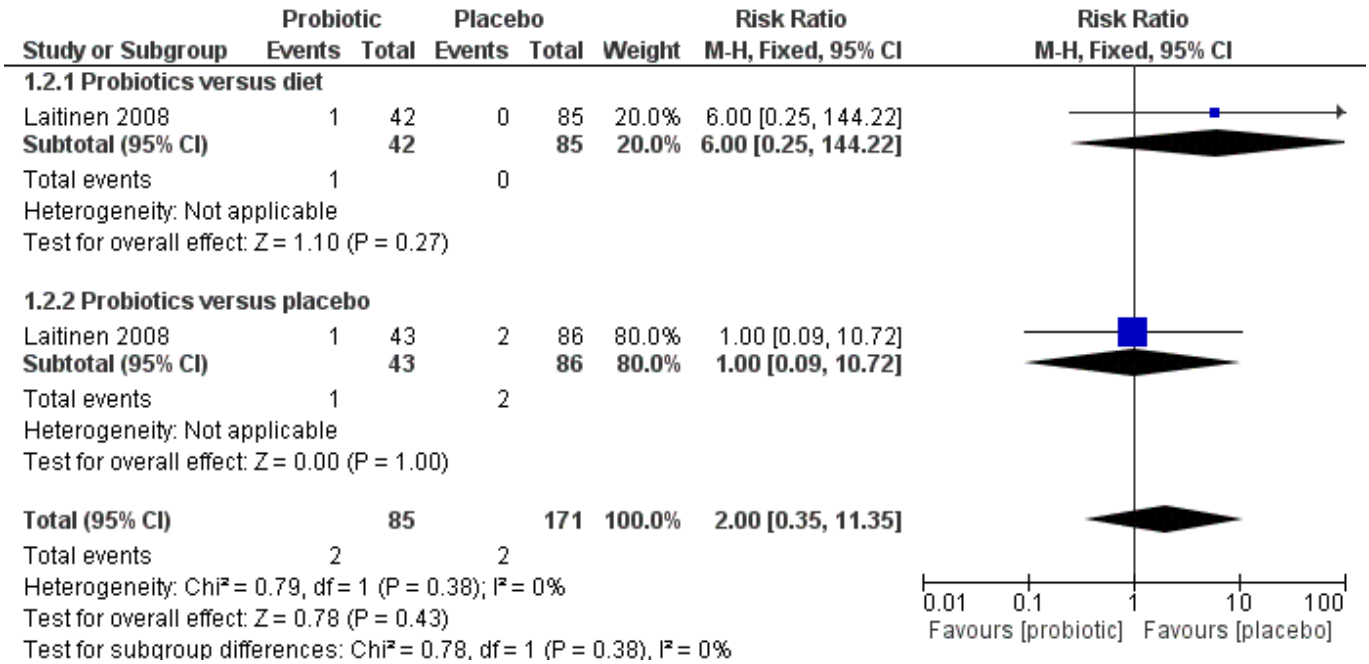


Infant outcome

Death (including miscarriage/IUFD/stillbirth/neonatal death)

The use of probiotics did not alter the rates of death at any stage of the pregnancy or in early infancy (RR 2.00, 95% CI 0.35 to 11.35) (Analysis 1.2) (Figure 3).

Figure 3. Forest plot of comparison: 1 Primary maternal and infant outcomes: Probiotics vs placebo or diet, outcome: 1.2 Miscarriage/IUFD/Stillbirth/Neonatal death.



Macrosomia/large-for-gestational-age babies

This outcome was not assessed (Analysis 1.3).

Secondary outcomes

Maternal outcomes

Rates of pre-eclampsia.

This outcome was not reported on (Analysis 2.1).

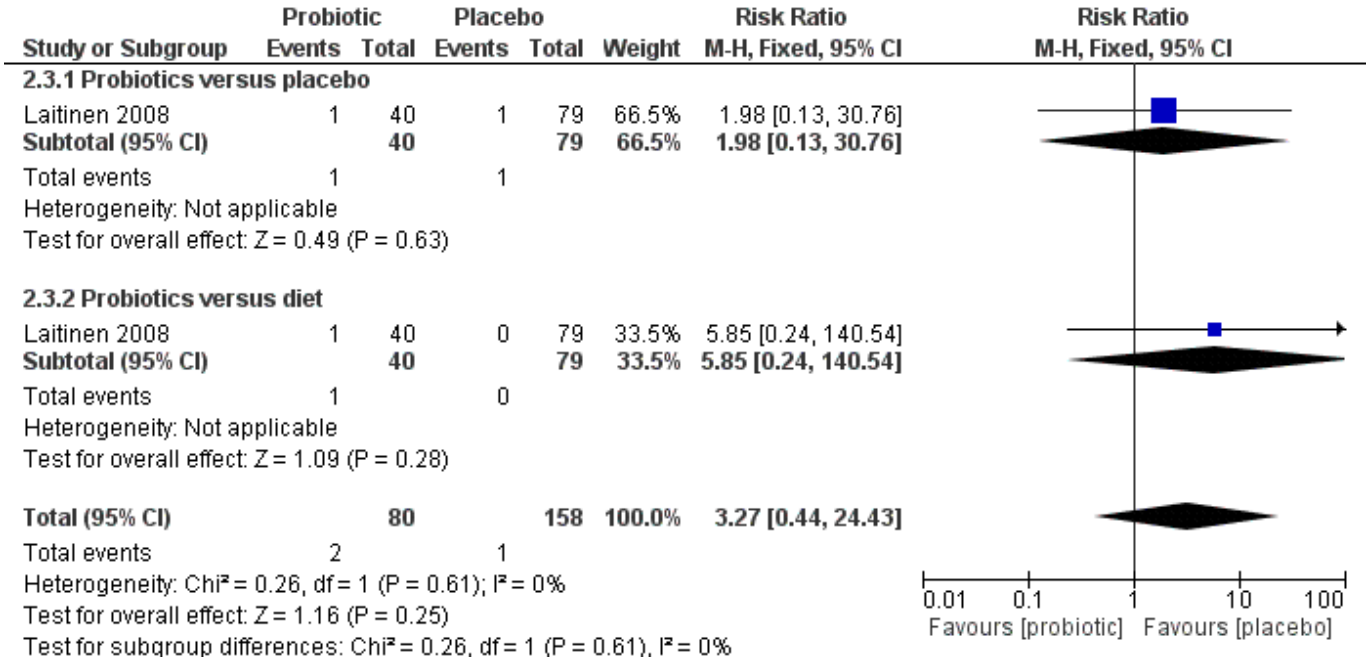
Maternal gestational weight gain

This outcome was not reported on (Analysis 2.2).

Preterm delivery

The use of probiotics did not affect the rates of preterm delivery (RR 3.27, 95% CI 0.44 to 24.43) (Analysis 2.3) (Figure 4) .

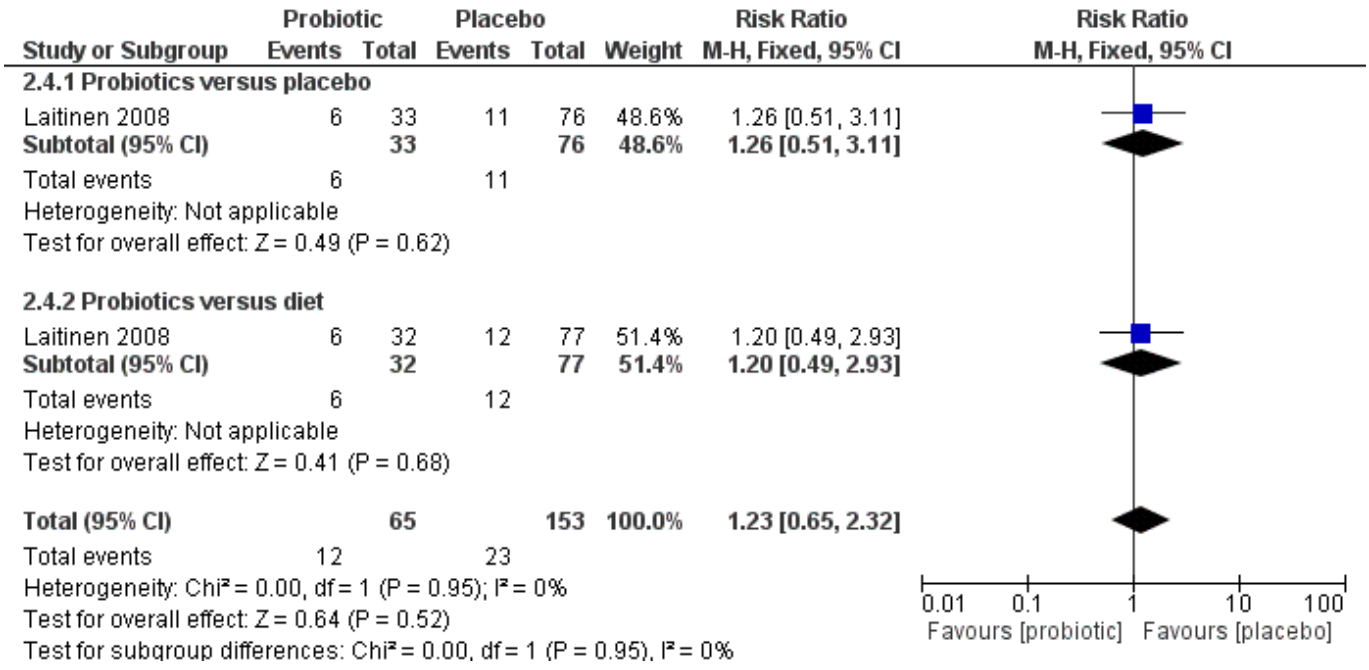
Figure 4. Forest plot of comparison: 2 Secondary maternal outcomes: probiotics vs placebo or diet, outcome: 2.3 Preterm delivery < 37 weeks' gestation.



Caesarean section

Probiotic supplementation did not change the rate of caesarean section (RR 1.23, 95% CI 0.65 to 2.32) (Analysis 2.4) (Figure 5).

Figure 5. Forest plot of comparison: 2 Secondary maternal outcomes: probiotics vs placebo or diet, outcome: 2.4 Caesarean section.



Long-term risk of diabetes mellitus

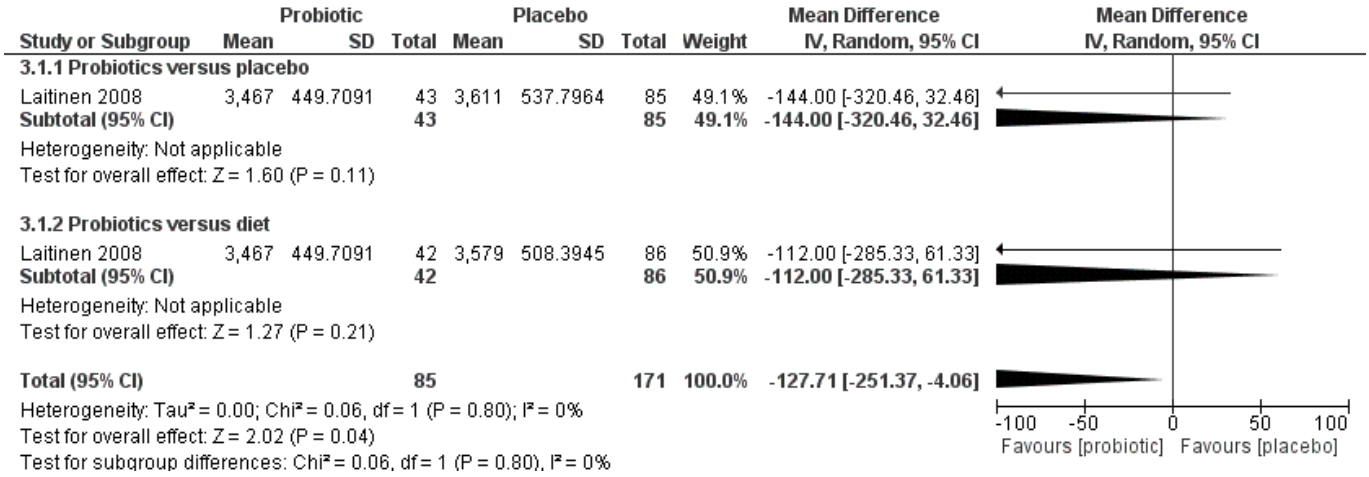
This outcome was not reported on (Analysis 2.5).

Infant outcomes

Infant birthweight, birth centile and body composition

Infant birthweight was assessed and there was a reduction of birthweight in the women taking probiotics supplementation (mean difference (MD) -127.71 g, 95% CI -251.37 to -4.06) (Analysis 3.1) (Figure 6). Birth centile (Analysis 3.2) and infant body composition Analysis 3.3 were not reported on.

Figure 6. Forest plot of comparison: 3 Secondary infant outcomes: probiotics vs placebo or diet, outcome: 3.1 Birthweight.



Shoulder dystocia

This outcome was not reported (Analysis 3.4).

Admission to neonatal intensive care unit

This outcome was not reported (Analysis 3.5).

Jaundice

This outcome was not reported (Analysis 3.6).

Hypoglycaemia

This outcome was not reported (Analysis 3.7).

Long-term outcomes

The outcomes childhood obesity (Analysis 3.8), rate of diabetes mellitus (Analysis 3.9) and childhood body composition (Analysis 3.10) were not reported in the included study.

DISCUSSION

Summary of main results

We included one study, involving 256 women. However, this study does show a 60% decrease in the rate of diagnosis of gestational diabetes mellitus in women taking probiotics from early pregnancy. No further analysis was done at this time due to there being only one completed study. No subgroup analyses have been undertaken as yet for the same reason. This will be addressed when the results of the ongoing studies are reported.

Overall completeness and applicability of evidence

The one completed study (Laitinen 2008) reported multiple maternal and infant outcomes across their various publications. They did not report on all the primary and secondary outcome measures to be included in this systematic review.

Quality of the evidence

The one study completed (Laitinen 2008) is a double blind, randomised trial of 256 women who were followed up for 12 months postpartum. The positive results of this study require confirmation with other studies also in populations at increased risk for developing gestational diabetes mellitus. There are four studies currently ongoing.

Potential biases in the review process

This review addresses a new area of research with only a limited number of studies identified. The search for studies in this area was performed using the Cochrane Pregnancy and Childbirth Group's Trials Register which is updated weekly to monthly with information from the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, handsearches from 30 journals and conference proceeding of major conferences and alerts for a further 44 journals. It is unlikely that studies that have concluded have been missed, however, ongoing studies that have not been registered in clinical trial registries could be missing. This would not alter the conclusion of the current review since there would not be any results to analyse yet. There was a low risk of bias within the one completed study for selection bias, performance bias, reporting bias and attrition bias. The data were extracted from the six publications relating to this study, however, the investigators were not contacted to obtain additional data. The data analysis for this study has necessarily been limited until further studies with relevant outcomes are reported.

Agreements and disagreements with other studies or reviews

Since this review addresses a new area of research, there have only been two reviews of the impact of probiotics on gestational diabetes mellitus, one written by the authors of this review (Barrett 2012) and one with a broader focus on maternal outcomes (Lindsay 2013). The inclusion criteria were slightly different between the reviews but the outcomes reported are in agreement with the ones reported in this Cochrane review.

AUTHORS' CONCLUSIONS

Implications for practice

The results from the included study (involving 256 women) suggest that probiotics may reduce the risk of gestational diabetes mellitus. This requires confirmation with further studies and especially in populations with higher risks of developing gestational diabetes mellitus. There are inadequate data to determine the effect of probiotics on fetal or neonatal death and macrosomia.

Implications for research

Further studies are needed to confirm the results of Laitinen 2008. Probiotics may have beneficial effects on other outcomes than gestational diabetes mellitus such as rates of macrosomia/large-for-gestational-age infants, infant body composition, maternal pre-eclampsia, delivery by caesarean section, and future risk of metabolic disease for mother and infant. These outcomes should be addressed in further studies. Potential additional aspects to be addressed in future studies include dosage of the probiotics, strain specificity, storage conditions and shelf life of the probiotics.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Laitinen 2008

Methods	DESIGN: randomised controlled trial. BLINDING: double blind for probiotics/placebo, single blind for dietary intervention. UNIT OF COMPARISON: individuals. DURATION: supplementation with probiotic/placebo from early pregnancy until the end of exclusive breastfeeding. FOLLOW-UP: 24 months postpartum. LOCATION: Finland.
Participants	TOTAL NUMBER: 256. No metabolic or chronic diseases. 7% of women were obese, 21% were overweight.
Interventions	PROBIOTIC: *Lactobacillus rhamnosus* GG, ATCC 53 103, Valio Ltd, Helsinki, Finland and *Bifidobacterium lactis* Bb12, Chr. Hansen, Hoersholm, Denmark, 10^{10} colony-forming units/d each). PLACEBO: microcrystalline cellulose and dextrose anhydrate. DIETARY: intensive dietary counselling aiming to conform to currently recommended pregnancy diet.
Outcomes	PRIMARY: maternal glucose metabolism as measured by plasma glucose, blood HbA1c, serum insulin and HOMA and QUICKI indices at baseline, third trimester of pregnancy, 1, 6 and 12 months postpartum.

Laitinen 2008 *(Continued)*

Notes	NCT00167700

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated block randomisation of 6 women. The use of only 1 block size could make it possible to guess the randomisation of the dietary intervention of the last individuals of each block. However, since this randomisation was only blinded to the participants and not the study personnel, the selection bias risk is still considered to be low.
Allocation concealment (selection bias)	Low risk	Randomisation list generated by a non-investigator statistician, sealed envelopes.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo/probiotic allocation was blind to both participants and personnel, dietary therapy was not blinded to personnel.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All personnel who handled or analysed blood samples were blind to the intervention.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Minimal loss to follow-up by assessment of glucose tolerance. Total loss to follow-up was 18.75% by 1 year postpartum.
Selective reporting (reporting bias)	Low risk	Reported all outcomes they intended to report.
Other bias	Low risk	No other biases detected.

Hb: haemoglobin
HOMA: homeostasis model assessment
QUICKI: quantitative insulin sensitivity check index

Characteristics of ongoing studies *[ordered by study ID]*

Ahmed 2012

Trial name or title	Probiotics (*Lactobacillus Rhamnosus*) in reducing glucose intolerance during and after pregnancy (GRIP).
Methods	DESIGN: randomised controlled trial. BLINDING: double blind for probiotics/placebo. DURATION: supplementation with probiotic/placebo from early pregnancy until delivery. FOLLOW-UP: 6 weeks postpartum. LOCATION: Pakistan.
Participants	Women in early pregnancy, 18-45 years with 1 or more of: BMI > 23 OR family history of diabetes in first-degree relatives, or maternal age > 35.
Interventions	PROBIOTIC: *Lactobacillus rhamnosus* 10^{10} colony-forming units/d each.

Ahmed 2012 *(Continued)*

Outcomes	Glucose tolerance by OGTT using ADA guidelines between 24-28 weeks' gestation and at 6-8 weeks' postpartum.
Starting date	October 2011.
Contact information	Principal Investigator: Bilal Ahmed, MSc, Aga Khan University.
Notes	NCT01436448

Callaway 2012

Trial name or title	SPRING: an RCT study of probiotics in the prevention of gestational diabetes mellitus in overweight and obese women.
Methods	DESIGN: randomised controlled trial. BLINDING: double blind for probiotics/placebo. DURATION: supplementation with probiotic/placebo from early pregnancy until delivery. LOCATION: Australia.
Participants	Overweight and obese women, < 16 weeks' gestation at study entry, 18-45 years.
Interventions	PROBIOTIC: *Lactobacillus rhamnosus* GG and *Bifidobacterium lactis* Bb12, Chr. Hansen, Hoersholm, Denmark, 10^9 colony-forming units/d each). PLACEBO: microcrystalline cellulose and dextrose anhydrate.
Outcomes	Glucose tolerance by OGTT using IADPSG guidelines between 24-28 weeks' gestation.
Starting date	November 2012.
Contact information	A/Prof Leonie Callaway, The University of Queensland.
Notes	ACTRN12611001208998

McAuliffe 2012

Trial name or title	Probiotics in Pregnancy Study (ProP Study).
Methods	DESIGN: randomised controlled trial. BLINDING: double blind for probiotics/placebo. DURATION: supplementation with probiotic/placebo from early pregnancy until delivery. LOCATION: Ireland.
Participants	1) Part A: Prevention of GDM: obese women aged 18-45 years, < 22 weeks' gestation. 2) Part B: Treatment of GDM: women with GDM or Impaired glucose tolerance, any BMI, aged 18-45 years, < 36 weeks' gestation.
Interventions	PROBIOTIC:

McAuliffe 2012 *(Continued)*

	PLACEBO:
Outcomes	1) Part A: difference between the control and probiotic groups in fasting blood glucose. 2) Part B: difference between the control and probiotic groups in fasting blood glucose.
Starting date	20/02/2012.
Contact information	Prof Fionnuala McAuliffe.
Notes	ISRCTN97241163

Wickens 2012

Trial name or title	A randomised placebo-controlled trial of the effects of the probiotic *Lactobacillus rhamnosus* HN001 taken from the 1st trimester of pregnancy till 6 months postpartum, if breastfeeding, on the development of eczema and atopic sensitisation in infants by age 12 months. (PIP)
Methods	DESIGN: randomised controlled trial. BLINDING: double blind for probiotics/placebo. DURATION: supplementation with probiotic/placebo from early pregnancy until 6 months postpartum. LOCATION: New Zealand.
Participants	Women 14-16 weeks' gestation, if they or the infant's father has a history of asthma, eczema or allergic rhinitis. No weight or age limits.
Interventions	PROBIOTIC: *Lactobacillus rhamnosus* HN001 administered daily as capsules. The starting viable cell number is $6.1x10^{10}$ CFU* per g, which equates to a dose per capsule of $9.2x10^{9}$ CFU. PLACEBO: the placebo will be identical in appearance and smell and contain maltodextran only.
Outcomes	PRIMARY: infant eczema and atopic sensitisation at age 12 months. SECONDARY: gestational diabetes mellitus (OGTT 75g using ADIPS criteria), bacterial vaginosis, group B strep, breast milk cytokines, maternal and infant anthropometry, maternal lipids and incretin hormones.
Starting date	20/12/2012.
Contact information	Dr Kristin Wickens, University of Otago, New Zealand.
Notes	ACTRN12612000196842

AFA: American Diabetes Association
ADIPS: Australasian Diabetes in Pregnancy Society
BMI: body mass index
CFU: colony forming unit
GDM: gestational diabetes mellitus
IADPSG: International Association of the Diabetes and Pregnancy Study Groups
OGTT: oral glucose tolerance test
RCT: randomised controlled trial

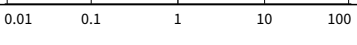
DATA AND ANALYSES

Comparison 1. Primary maternal and infant outcomes: probiotics versus placebo or diet

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Diagnosis of gestational diabetes	1	225	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.20, 0.70]
1.1 Probiotics versus placebo	1	111	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.16, 0.92]
1.2 Probiotics versus diet	1	114	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.15, 0.89]
2 Miscarriage/IUFD/Stillbirth/Neonatal death	1	256	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.35, 11.35]
2.1 Probiotics versus diet	1	127	Risk Ratio (M-H, Fixed, 95% CI)	6.0 [0.25, 144.22]
2.2 Probiotics versus placebo	1	129	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.09, 10.72]
3 Macrosomia	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.1 Probiotics versus placebo	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Probiotics versus diet	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

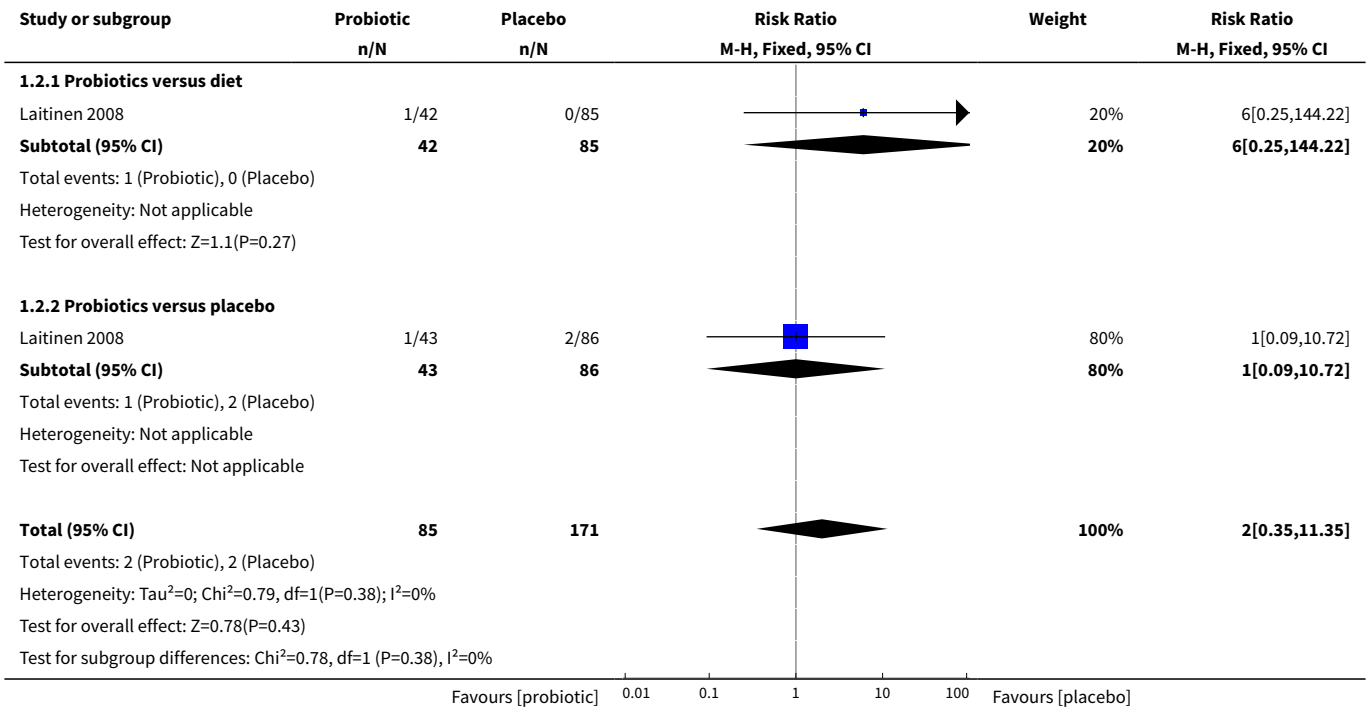
Analysis 1.1. Comparison 1 Primary maternal and infant outcomes: probiotics versus placebo or diet, Outcome 1 Diagnosis of gestational diabetes.

Study or subgroup	Probiotic n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 Probiotics versus placebo					
Laitinen 2008	5/38	25/73		48.74%	0.38[0.16,0.92]
Subtotal (95% CI)	**38**	**73**		**48.74%**	**0.38[0.16,0.92]**
Total events: 5 (Probiotic), 25 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.14(P=0.03)					
1.1.2 Probiotics versus diet					
Laitinen 2008	5/38	27/76		51.26%	0.37[0.15,0.89]
Subtotal (95% CI)	**38**	**76**		**51.26%**	**0.37[0.15,0.89]**
Total events: 5 (Probiotic), 27 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.23(P=0.03)					
Total (95% CI)	**76**	**149**		**100%**	**0.38[0.2,0.7]**
Total events: 10 (Probiotic), 52 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=0.95); I^2=0%					
Test for overall effect: Z=3.09(P=0)					
Test for subgroup differences: Chi^2=0, df=1 (P=0.95), I^2=0%					



Favours [probiotic] Favours [placebo]

Analysis 1.2. Comparison 1 Primary maternal and infant outcomes: probiotics versus placebo or diet, Outcome 2 Miscarriage/IUFD/Stillbirth/Neonatal death.



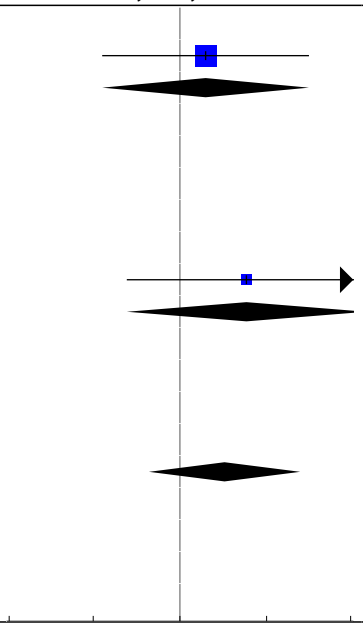
Comparison 2. Secondary maternal outcomes: probiotics versus placebo or diet

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pre-eclampsia	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.1 Probiotics versus placebo	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Probiotics versus diet	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Gestational weight gain	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.1 Probiotic versus placebo	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Probiotic versus diet	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Preterm delivery < 37 weeks' gestation	1	238	Risk Ratio (M-H, Fixed, 95% CI)	3.27 [0.44, 24.43]
3.1 Probiotics versus placebo	1	119	Risk Ratio (M-H, Fixed, 95% CI)	1.98 [0.13, 30.76]
3.2 Probiotics versus diet	1	119	Risk Ratio (M-H, Fixed, 95% CI)	5.85 [0.24, 140.54]
4 Caesarean section	1	218	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.65, 2.32]
4.1 Probiotics versus placebo	1	109	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [0.51, 3.11]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.2 Probiotics versus diet	1	109	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.49, 2.93]
5 Maternal diagnosis of diabetes mellitus postpartum	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.1 Probiotics versus placebo	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 Probiotics versus diet	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

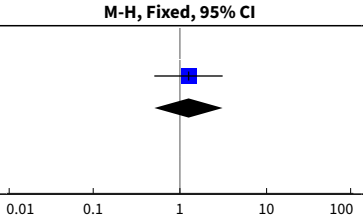
Analysis 2.3. Comparison 2 Secondary maternal outcomes: probiotics versus placebo or diet, Outcome 3 Preterm delivery < 37 weeks' gestation.

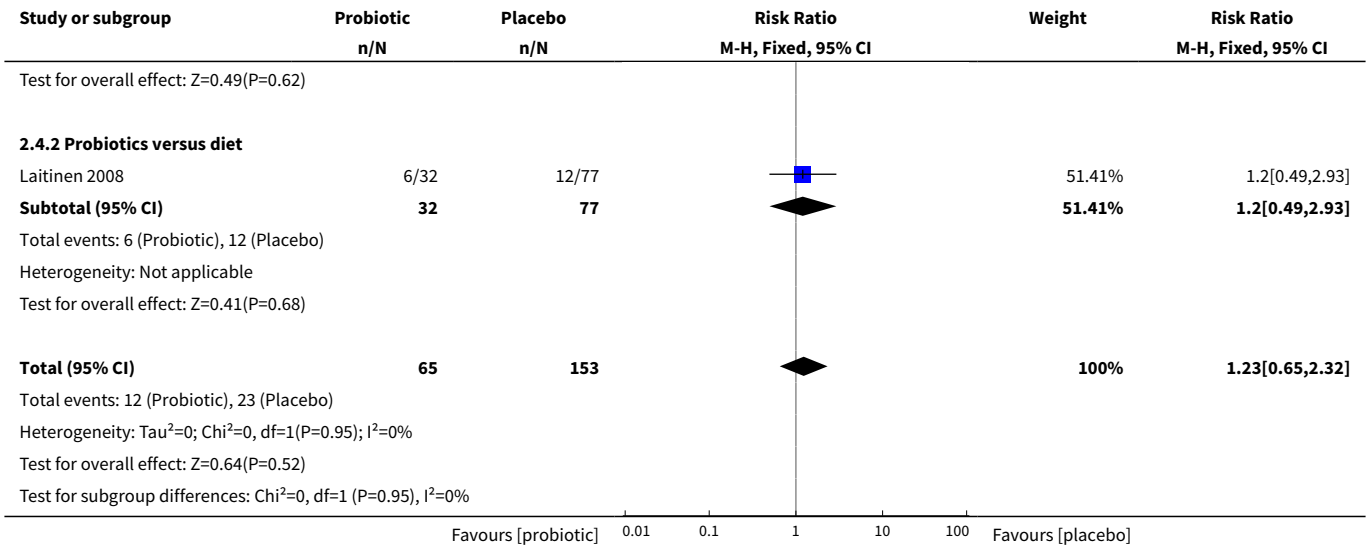
Study or subgroup	Probiotic n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.3.1 Probiotics versus placebo					
Laitinen 2008	1/40	1/79		66.49%	1.98[0.13,30.76]
Subtotal (95% CI)	**40**	**79**		**66.49%**	**1.98[0.13,30.76]**
Total events: 1 (Probiotic), 1 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.49(P=0.63)					
2.3.2 Probiotics versus diet					
Laitinen 2008	1/40	0/79		33.51%	5.85[0.24,140.54]
Subtotal (95% CI)	**40**	**79**		**33.51%**	**5.85[0.24,140.54]**
Total events: 1 (Probiotic), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.09(P=0.28)					
Total (95% CI)	**80**	**158**		**100%**	**3.27[0.44,24.43]**
Total events: 2 (Probiotic), 1 (Placebo)					
Heterogeneity: Tau²=0; Chi²=0.26, df=1(P=0.61); I²=0%					
Test for overall effect: Z=1.16(P=0.25)					
Test for subgroup differences: Chi²=0.26, df=1 (P=0.61), I²=0%					



Analysis 2.4. Comparison 2 Secondary maternal outcomes: probiotics versus placebo or diet, Outcome 4 Caesarean section.

Study or subgroup	Probiotic n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.4.1 Probiotics versus placebo					
Laitinen 2008	6/33	11/76		48.59%	1.26[0.51,3.11]
Subtotal (95% CI)	**33**	**76**		**48.59%**	**1.26[0.51,3.11]**
Total events: 6 (Probiotic), 11 (Placebo)					
Heterogeneity: Not applicable					





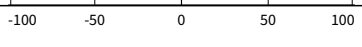
Comparison 3. Secondary infant outcomes: probiotics versus placebo or diet

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Birthweight	1	256	Mean Difference (IV, Random, 95% CI)	-127.71 [-251.37, -4.06]
1.1 Probiotics versus placebo	1	128	Mean Difference (IV, Random, 95% CI)	-144.0 [-320.46, 32.46]
1.2 Probiotics versus diet	1	128	Mean Difference (IV, Random, 95% CI)	-112.0 [-285.33, 61.33]
2 Birthweight centile	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.1 Probiotics versus placebo	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Probiotics versus diet	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Percentage body fat (neonatal)	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.1 Probiotics versus placebo	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Probiotics versus diet	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Shoulder dystocia	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.1 Probiotics versus placebo	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

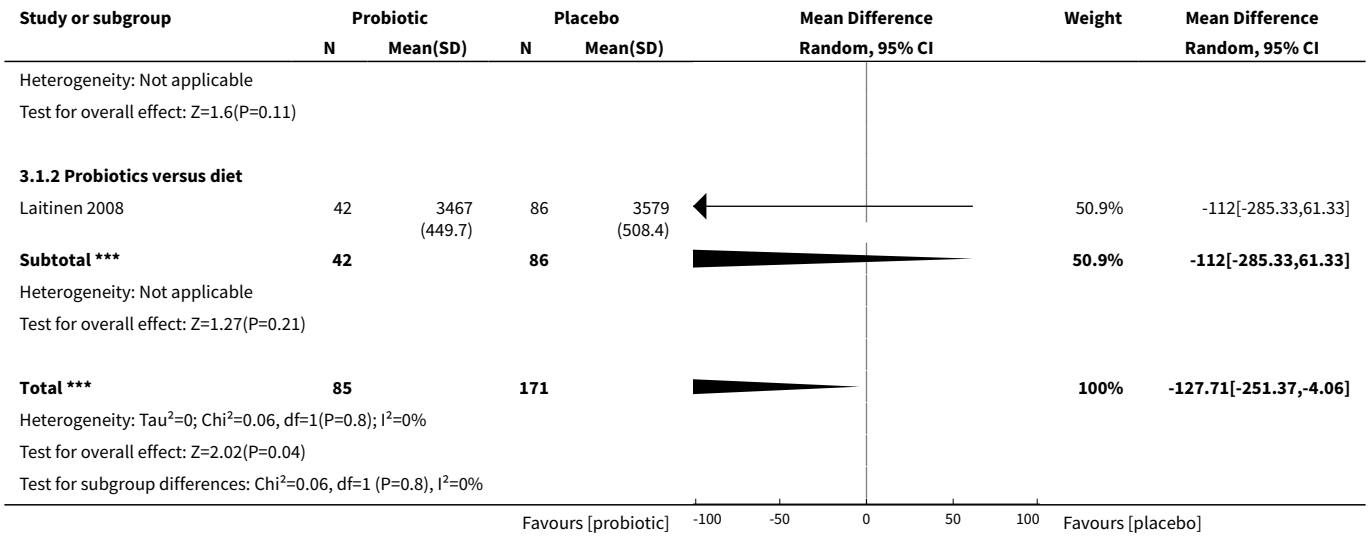
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
4.2 Probiotics versus diet	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Admission to neonatal intensive care	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.1 Probiotics versus placebo	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 Probiotics versus diet	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Jaundice	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.1 Probiotics versus placebo	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 Probiotics versus diet	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Hypoglycaemia	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.1 Probiotics versus placebo	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 Probiotics versus diet	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Childhood obesity	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.1 Probiotics versus placebo	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.2 Probiotics versus diet	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 Infant diagnosis of diabetes mellitus	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.1 Probiotics versus placebo	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.2 Probiotics versus diet	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10 Percentage body fat (childhood)	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.1 Probiotics versus placebo	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.2 Probiotics versus diet	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 3.1. Comparison 3 Secondary infant outcomes: probiotics versus placebo or diet, Outcome 1 Birthweight.

Study or subgroup	Probiotic N	Probiotic Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
3.1.1 Probiotics versus placebo							
Laitinen 2008	43	3467 (449.7)	85	3611 (537.8)		49.1%	-144[-320.46,32.46]
Subtotal ***	**43**		**85**			**49.1%**	**-144[-320.46,32.46]**



Favours [probiotic] Favours [placebo]



ADDITIONAL TABLES

Table 1. Diagnostic criteria for GDM

	IADPSG (ACOG Committee 2005) #	ADIPS ## (Hoffman 1998)	ADA ### (ADA criteria)
OGTT (g)	75	75	100
Fasting (mmol/L)	5.11	5.5	5.33
1 Hour (mmol/L)	10	-	10
2 Hour (mmol/L)	8.5	8 *	8.6
3 Hour (mmol/L)	-	-	7.8

International Association of the Diabetes and Pregnancy Study Groups has separate criteria for diabetes diagnosed during pregnancy (as compared to gestational diabetes) to differentiate cases where diabetes is probably pre-existing and does not resolve postpartum.
Australasian Diabetes in Pregnancy Society
American Diabetes Association
OGTT: oral glucose tolerance test
* In New Zealand, the 2-hour post glucose diagnostic cut-off is 9 mmol/L

CONTRIBUTIONS OF AUTHORS

Helen Barrett and Marloes Dekker Nitert developed the protocol. Louise Callaway and Leonie Conwell edited and commented on the protocol. Helen Barrett and Marloes Dekker Nitert wrote the review, assessed the citations and studies found for inclusion, risk of bias and data analysis. Leonie Callaway and Louise Conwell assisted with data interpretation, and edited and commented on the review.

DECLARATIONS OF INTEREST

Louise Conwell - none known.

Leonie Callaway, Marloes Dekker Nitert and Helen Barrett are investigators in a trial examining the use of probiotics for preventing gestational diabetes mellitus (Callaway 2012) - Leonie Callaway is the primary investigator of this trial. In future updates of this review, these investigators will not be involved in any decisions relating to their trial: assessment of the trial for inclusion, assessment of risk of bias

and data extraction will be carried out by individuals who are not directly involved in the trial. Louise Conwell (review author) and a third party will carry out these tasks.

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- The University of Queensland, School of Medicine, Australia.

  salary

External sources

- Royal Brisbane and Women's Hospital, Foundation, Australia.

  salary

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None.

INDEX TERMS

Medical Subject Headings (MeSH)

Diabetes, Gestational [*prevention & control]; Probiotics [*therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans; Pregnancy